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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,769	07/28/2006	Sami Saribas	019957-016830US	2116

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
MEAH, MOHAMMAD Y	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,769	SARIBAS ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,7-11 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7-11 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/25/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election with traverse of group I (claims1-3, 5, 7-11 and 14) in their response of 05/12/2008 is acknowledged. The traversal is on the ground(s) that groups I-VII inventions comprise method steps not the protein and therefore linked by a special technical feature. Applicants' arguments are fully considered but they are found unpersuasive because WO20040099231 not only teach glycosyltransferase including, ST3Gal3 comprising tag peptide of maltose binding domain but also state that glycosyltransferase comprising MBD facilitate in purification step and also stated refolding of the soluble protein in refolding reagent (such as GSH).

Therefore the restriction is maintained and made FINAL.

Sequence compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that variety of sequences are recited in the specification see for example page 78, pargh. 0332 and in the drawing, figures 6-14, figures 24A-B, 26A-B, 30, 35, 38A-C, 41-44 without being identified by any sequence listing. Applicant is required to identify all sequences by a SEQ ID NO in the figures or the specification. Appropriate correction is required. See particularly 37 CFR 1.821(d).

Priority

This application is filed under 35 USC 371 of PCT/US05/03856, filed 02/04/2005, which claims priority to U.S. Provisional Application No. 60/542,210, filed February 4, 2004, and of U.S. Provisional Application No. 60/599,406, filed August 6, 2004, and of U.S. Provisional Application No. 60/627,406, filed November 12, 2004;

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 06/25/2007 and is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the IDS statements.

Claim Rejections

35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

Obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 7, 10-11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paulson et al (US patent 5858751) in view of Hellman et al (protein expr, pur. 1995, 6, 56-62, from IDS) and Clark et al (Current opin. Biotech. 2001, 202-207, from IDS).

Claims 1 is directed to method of refolding insoluble eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) protein by solubilizing in a solubilizing buffer and refolding using a refolding buffer comprising a redox couple wherein the refolded ST3Gal3 catalyzes the transfer of sialic acid sugar from a donor to an acceptor substrate. Claim 2 directed to the method of claim 1 wherein said eukaryotic ST3Gal3 is truncated to remove all or portion of stem region. Claim 7 is directed to the method of claim 1 wherein said eukaryotic ST3Gal3 is expressed in a bacterial host cell as an insoluble inclusion body. Claim 10 is directed to the method of claim 1 wherein said eukaryotic ST3Gal3 is refolded by using GSH/GSSG. Claim 11 is directed to the method of claim 1 wherein said acceptor is protein, peptide glycoprotein or glycopeptides. Claim 14 is directed to the method of claim 1 wherein said donor substrate is CMP sialic acid.

Paulson et al. teach multiple methods and expression of various eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) in prokaryotic organisms (whole document,) including expression of mutated proteins particularly derivatives lacking stem region (column 75, claim 4) and teach the transferring sialic acid from cmp-sialic acid donor (column 7 lines 15-20) to glycoprotein (column 4 lines 22-30). Paulson is silent regarding maltose binding and the refolding of the alpha(2,3) sialyltransferease (ST3Gal3) using a buffer comprising redox system.

Clark et al teach method of isolation, purification and refolding of insoluble protein from inclusion bodies (page 202, column 2) using disulfide bond forming redox buffer such as GSH/GSSG (page 205, column 1). Clark does not teach

refolding alpha(2,3) sialyltransferease (ST3Gal3) nor teach fusion protein comprising maltose binding domain.

Hellman et al teach solubilizing insoluble protein from inclusion bodies by expression of N-terminal fusion of desired protein with maltose binding domain (MBD) (such as, MBD fusion of CGT(cyclomaltodextrin glucanotransferase, see page 60, column 2).

It would have been obvious to one of ordinary skill in the art to combine the teachings of Paulson et al., Hellman et al and Clark et al) to produce biologically active soluble eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) by expressing in a prokaryotic organism a fusion protein consisting ST3Gal3 and the well known purification MBD tag, solubilize from the inclusion bodies and refold using refolding buffer. One of ordinary skill in the art would have been motivated to do so because eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) are used in the production of other glycosylated proteins and/or specific oligosaccharides that are useful as pharmaceuticals for the treatment of various disorders (Paulson et al column 2 lines 38-68). One of ordinary skill in the art would have been also motivated to express the eukaryotic alpha (2, 3) sialyltransferease in prokaryotic system because i) use of prokaryotes in recombinant production proteins are well known in the art, ii) prokaryotic system commercially viable (cheaper to produce), iii) easy to handle and purify recombinant proteins of interest from prokaryotes, iv) prokaryotic systems are potentially free of eukaryotic pathogens. Therefore a skilled artisan would be motivated to employ the prokaryotic recombinant expression system described (Paulson et al) to

produce alpha (2, 3) sialyltransferease (ST3Gal3) on a large scale and apply the method of Hellman et al (applying MBD fusion) and Clark et al to refold (using redox buffer such as GSH/GSSG) the said protein in an active form so that it catalyzes the transfer of sialic acid sugar from a CMP-sialic acid to galactose containing substrate. The expectation of success is high, because the above cited references define the status of the prior art in the successful method of expression, isolation, solubilization and refolding of sialyltransferase from inclusion body of prokaryotes expression system.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paulson et al (US patent 5858751) in view of Hellman et al (protein expr, pur. 1995, 6, 56-62, from IDS) and Clark et al (Current opin. Biotech. 2001, 202-207, from IDS) and further in view of Ramakrishnan et al (J. Biol. Chem. 2001, 276, 37665-37671)

The teachings of Paulson et al., Hellman et al and Clark et al are summarized above.

Ramakrishnan et al teach mutation of unpaired cysteine, Cys342 to Thr of a beta-galacotosyltransferase resulted 2 to 3 fold increase in yield of refolded enzyme (compare to unmutated enzyme, page 37666, 1st column last pargh).

It would have been further obvious to one of ordinary skill in the art to combine the teachings of Paulson et al., Hellman et al and Clark et al with the teaching of Ramakrishnan et al to produce biologically active soluble eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) in high yield by expressing in prokaryotic organism a fusion protein consisting of ST3Gal3 having mutation of

unpaired cysteine residue(s) (as taught Ramakrishnan et al) and the well known MBD tag, solubilize from the inclusion bodies and refold using refolding buffer in order to get better yield of refolded protein.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Paulson et al (US patent 5858751) in view of Hellman et al (protein expr, pur. 1995, 6, 56-62, from IDS), Clark et al Current opin. Biotech. 2001, 202-207, from IDS) and further in view of Nilsson et al. (Protein expression and purification 1997, 11, pp 1-16, IDS).

Claim 5 is directed to the method of claim 1 wherein said eukaryotic ST3Gal3 further comprise purification domain selected from the group consisting of a starch binding domain, a thioredoxin domain, and poly-his domain.

The teachings of Paulson et al., Hellman et al and Clark et al are summarized above.

It is well known in prior art that a convenient method of purification of protein is make a fusion protein wherein target protein is fused with one or more affinity tags (such as one or more affinity tags from the group of maltose binding domain, starch binding domain, a thioredoxin domain, glutathione-S-transferase (GST) domain and poly-HIS domain, Nilsson et al.). Nilsson et al. teach the use of two affinity tags attached to target protein (table 2, GST and Poly-HIS domains, page 5, 1st column 2nd pargh.) and purify the target protein using two affinity columns (Fig 4 at page 8).

It would have been further obvious to one of ordinary skill in the art to combine the teachings of Paulson et al., Hellman et al and Clark et al to produce

biologically active soluble eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) by expressing in prokaryotic organism a fusion protein consisting of ST3Gal3 and the well known purification MBD tag with the teaching of Nilsson et al. to add second purification tag such as, poly-HIS domain , solubilize said protein having MBD tag and 2nd purification tag from the inclusion bodies and refold using refolding buffer and purify by using two affinity columns so that said purified ST3Gal3 catalyzes the transfer of sialic acid sugar from a CMP-sialic acid to galactose containing substrate.

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paulson et al (US patent 5858751) in view of Hellman et al (protein expr, pur. 1995, 6, 56-62, from IDS) and Clark et al Current opin. Biotech. 2001, 202-207, from IDS).

Claims 8-9 are directed to the method of claim 1 wherein one or two additional recombinant eukaryotic glycosyltransferases is (are) refolded with said eukaryotic ST3Gal3.

The teachings of Paulson et al., Hellman et al and Clark et al are summarized above.

It is well known in prior art that most bioactive glycoproteins comprise variety of sugar residues and needs multienzymes to produce them (see Paulson et al column 4 lines 21- 44). It would have been further obvious to one of ordinary skill in the art, for the production of a multienzymes system to catalyze the transfer (in addition to sialic acid sugar) sugar moieties from donors to acceptor substrate, combine the teachings of Paulson et al., Hellman et al and Clark et al

to produce biologically active soluble eukaryotic alpha (2, 3) sialyltransferease (ST3Gal3) by expressing in prokaryotic organism a fusion protein consisting ST3Gal3 and the well known MBD purification tag, solubilize from the inclusion bodies and further refold 2 or more glycosyltransferase with it using refolding buffer so that said multienzymes system catalyzes the transfer (in addition to sialic acid sugar) other sugar moieties from donor to acceptor substrate.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah, PhD
Examiner, Art Unit 1652
Recombinant Enzymes, 3C31 Remsen Bld
400 Dulany Street, Alexandria, VA 22314
Telephone: 517-272-1261

/Nashaat T. Nashed/
Supervisory Patent Examiner, Art Unit 1652